Research Paper | Medical Science | E-ISSN No : 2454-9916 | Volume : 5 | Issue : 10 | Oct 2019

"THE NEW HUNT FOR KILLER VIRUS-HEPATITIS-B" (ELIMINATION OF VIRAL HEPATITIS, AN INFECTIOUS DISEASE PHYSICIAN'S PERSPECTIVE)

Raghavendra Rao M.V[1] | Dilip Mathai[1] | S. P. Pallavi[1] | Vijaya Raj URS[3] | Mahendra Kumar Verma[2] | J. Madhavi[2] | Ramanaiah C. Jagarlamudi[3] | Sowmya MK[4]

[1]Apollo Institute of Medical Sciences & Research, Telangana state, Hyderabad, India.
[2]Acharya Nagarjuna University, Guntur, AP, India.
[3]Amina Hospital,United Arab Emirates.
[4]Emirate Group of Hospitals, UAE.

ABSTRACT

Jaundice is a disease that your friends diagnose. Know safety. No infection. The liver is the largest internal organ in the body. Here, there and everywhere the Hepatitis B Virus (HBV) is present.

It is present at high levels in many different body fluids.Hepatitis has been a major plague of mankind. The clinical signs of HBV vary widely. Most cases are asymptomatic. However, sometimes fever, loss of appitite, abdominal discomfort, nausea, fatigue and other symptoms gradually appear.

Hepatitis B can cause mild illness lasting a few weeks, or it can lead to a serious, lifelong illness. The virus infects hepatic cells and causes liver tissue degeneration and release of liver associated enzymes (transaminases) into blood stream.This is followed by jaundice, accumulation of bilurubin (A black down product of hemoglobin) in skin and other tissues with resulting yellow appearance

KEYWORDS: Bilurubin, Cirrhosis, hepatocellular Carcinoma (HCC), HBsAg, Colo-Rectal Liver Metastases, Chronic hepatitis B (CHB), Seroprevalence.

INTRODUCTION:
Hepatitis was elevated to a higher priority with a goal of eliminating viral hepatitis as a public health threat by 2030.

The goal of the WHO is to achieve a 90% reduction in the incidence of chronic hepatitis B (CHB) and C infection by 2030.(1)

Chronic HBV infection is a major cause of liver cirrhosis and hepatocellular carcinoma (HCC) (2). Although universal hepatitis B virus (HBV) vaccination has been successfully applied worldwide and effective drugs for a long-term suppression of HBV have been extensively applied, chronic HBV infection remains a serious health problem in most countries because of the large number of subjects with chronic HBV infection living in most of the nations. Two billion people worldwide had contact with HBV,and nearly 240 million people had chronically HBV infected. (3)

While for individuals with HBV infection hepatitis B surface antigen (HBsAg) positive] there are well-standardized clinical and therapeutic strategies. In occult HBV infection patients (HBsAg-negative, anti-HBc negative and HBV-DNA positive) these strategies are not so well defined. (4) HBV reactivation, a phenomenon characterized by increased HBV-DNA serum values of about 1 log or by HBV DNA turning positive if previously undetectable in serum, mostly occurs in a context of temporary or permanent immunosuppressant. HBV reactivation in patients with occult HBV infection may also determine the reappearance of HBsAg in serum, possibly associated with an acute hepatic exacerbation characterized by an elevation in liver enzymes above the normal values and seldom by increased bilirubin levels. (5)

Some countries implemented universal infant vaccination strategies soon after the vaccine was developed in 1981.(6)

In 1997 infant vaccination coverage was highest in the Eastern Mediterranean (35%), Americas(28%), and Europe (23%) (7)

Appropriate donor selection and highly sensitive laboratory blood screening procedures for major transfusion-transmitted viral infections (HBV, HCV, and HIV) are two main measures to prevent transfusion of infected blood. Despite these methods, there is still a residual risk of entering infected donations to the blood supply. The greatest portion of the residual risk were due to donating blood in the infectious window period, the time between infections and detectability by screening tests. Elimination of these risks is essential to monitor and improve blood supply. In the past two decades, various mathematical models have been developed to calculate the residual risk. One of the most accepted models is that of the retrovirus donor study of US window period model, that has been used to estimate window period donation risk since early 1990 in the US, and now been applied successfully worldwide. (8)

Chronic hepatitis B is highly prevalent in China and the prevalence of hepatitis B virus infection is the highest of all countries globally. The prevalence of HBV surface antigen (HBsAg) positively in China was 8.8% in 1979, 9.8%,in 1992,and 7.2% in 2006 (9)

Several studies have reported the HBV infection reduced the risk of CRLM (Colo-Rectal Liver Metastases) (10)

Chronic hepatitis B (CHB), an adolescent viral infection, progress over decades to cirrhosis,liver failure,hepato cellular carcinoma and premature death (11)

In the USA, about 1800 death certificates annually list Hepatitis, as an outstanding or contributing cause of death.(12)

Manos et al. found that only 48% of the deaths that were identified HBV with chronic liver disease. Adults are known to have a high prevalence of CHB infections-including foreign-born Asian-Pacific islanders.(13)

Racial and ethnic minorities and adults diagnosed with sexually transmitted infections are often not screened for HBV as recommended.(14)
O.7% prevalence of HCV infection was observed among medicine and health science students of Wollo University, Northeast Ethiopia.(15)

Current treatments are limited to nucleotide analogs, which are direct-acting antivirals that block DNA synthesis, and interferon-α. Interferon-α produces its antiviral effects by several mechanisms.(16)

Non-viral causes such as toxins, drugs, autoimmune diseases, infections with bacteria, as well as parasites, can also lead to hepatitis.(17)

HBV is a partially double-stranded DNA virus that belongs to the Hepadnaviridae family, in the Orthohepadna virus genus. It is the causative agent of hepatitis B infection, resulting in both acute and chronic hepatitis infections. Chronic HBV infection can progress to hepatocellular carcinoma (HCC) and liver cirrhosis and subsequently leads to death. Therefore, it is considered a life-threatening virus worldwide, leading to significant rates of mortality. (18)

Chronic hepatitis B can cause liver cirrhosis and hepatocellular carcinoma and is responsible for more than 0.5–1.0 million deaths per year.Chronic HBV infection (CHBVI) and viral clearance are influenced by multiple genetic and environmental factors, including viral and host factors.(19)

Several loci, located in human leukocyte antigen-C (HLA-C) 9, HLA-DP10,

HLA-DQ11, HLA-DOA, complement factor B (CFB), NOTCH412, euchromatic histone lysine methyltransferase 2 (EHMT2), transcription factor 19 (TCF19)13, and two non-HLA loci, CD4012 and ubiquitin-conjugating enzyme E2 L3 (UBE2L3) , have been reported to be significantly associated with HBV-related diseases.(20)

HISTORY:
The hepatitis B virus has infected humans since at least the Bronze Age. (21)

It was also found that some ancient hepatitis viral strains still infect humans, while other became extinct.(22)

A mummified child in the Basilica, found that the virus was closely related to modern variants. (23)

A significant increase of HBV in the population was noted within the last 5,000 years.(24)

The human hepatitis virus originated from Chimpanzee, gorilla, orangutan, and gibbons species. (25)

The ancestral virus originated in Asia and spread to Greenland and then spread westward within the last 400 years.(26)

It was also found that some ancient hepatitis viral strains still infect humans, while other became extinct.(27)

Now much vaccine is produced using recombinant yeast cells containing the gene for the protein. (28)

One of the largest out breaks of HBV infections in Europe occurred in London 1998.A patient went to an alternative clinic and was treated with a technique called auto hemotherapy.This involved mixing a small sample of the patients blood with a saline,then injecting the blood and saline mixture into her buttocks or acupuncture points.She subsequently developed acute Hepatitis B and public health doctors were contacted and an investigation started having identified the practices in the clinic that could have resulted in her becoming jaundiced.(29)

MAJOR ADVANCES IN DISCOVERIES:
1. In 1957, interferon discovered.
2. In 1990-PMEA, Anti hepatitis-B and anti-HIV activity discovered
3. 1991-Interferon 2b approved for HBV
4. 1998-Entecavir, anti-HBV activity discovered
5. 1998-Lamivudine (3TC) approved as a first nucleoside analog for HBV
6. 2001-Telbuvudine anti-HBV activity discovered
7. 2002-Adefovir dipivoxil (PMEA) prodrug appeared for HBV
8. 2005-Entecavir and Peg interferon-alpha 2a approved for HBV
9. 2006-Telbuivudin approved for HBV
10. 2008-Tenofovir approved for HBV
11. 2010- Lamivudine patent expressed in Europe.

Although HB c Ag antigen is also present, antibody against it invariably occurs and prevents its detection.(30)

In the past decade significant advances have been made in treatment of HBV.Numerous agents which induce viral suppression effectionately slow the progression of liver disease.However not all those chronically infected therapy and is necessary to delineate strategies for both diagnosis and control reevaluation so as to decide on optimal management of the disease.

WHERE THE RESEARCH GO NEXT:
In the past CDC did not recommend pre vaccination screening for health care providers.In 2012,the CDC recommended that those at high risk for HBV infection.(eg.Those born in endemic regions of the world) under go pre vaccination testing for hepatitis B.(31)

.

Currently there are markers that can be used,but more work is needed to identify how to use these and new markers as end point of successful HBV therapy and what markers and drugs will be most benefit at which phase of CHB.(32)

BIOMARKERS:
1. HBV infection
2. HBsAg-Hepatitis B surface antigen,the envelope. protein consisting of three polypeptides
3. Ante HBs-Antibody to hepatitis core antigen
4. HbeAg- antigen associated with the nucleocapsid also found as soluble protein in serum.
5. Ante-Hbe-Antibody to hepatitis Be antigen.

THE SIGNIFICANT GAP IN RESEARCH:
Broadly there are two approaches to the prevention of infection with HBV.Modification of risk behavior and immunization measures for the former include avoiding unprotected sexual contact by the use of condoms and reducing needle sharing among injecting drug users through needle exchange schemes.Implimentation of sensible infection control policies can reduce the risks considerably to health care workers and patients.It is essential that blood for transfusion and organ donars for transplantation are screened.(33)

Mass-vaccination campaigns have resulted in decreases in hepatitis B surface antigen seroprevalence.(34)

Cirrhosis develops at an annual incidence of 8%-10% in patients with HBeAg negative chronic hepatitis and 2%-5% in patients with HBcAg positive chronic hepatitis. Cirrhosis is the major risk factor for the development of HCC; The annual incidence HCC is1% for HBV carriers without cirrhosis and 2%-3% for those with cirrhosis.The risk factor for cirrhosis and HCC are similar and include high HBV DNA levels HBcAg positivity, older age and male gender.(35)

Many known HCC-related deaths are miscoded in medical records and/or not noted on death certificates.(36)

DIAGNOSIS OF HBV INFECTION:
Among patients in ongoing medical care for testing less than half were subsequently tested for hepatitis.(37)

Patients diagnosed with CHB are unlikely to be followed optimally to detect the development of cirrhosis and hepato cellular carcinoma.(38)

Perinatal transmission of HBV can be prevented effectively if the HBs Ag positive mother is identified and if her infant receives appropriate immunoprophylaxis. Administration of HBIG and the first dose of HBV vaccine with 12 hrs of birth prevents the development of 90 % perinatal infections.(39)

Gene expressing profiling in liver may be useful for understanding features of distinct liver diseases and its study in early to advanced stages of chronic liver disease may prove useful guiding disease progression.Proteomics has been described as useful biomarker discovery tool and has become increasingly useful in the study of liver fibrosis.In addition,it can highlight alterationsorup regulation of various proteins during different stages of the disease.Thus the new techniques form useful adjuncts to routine histological assessment of liver biopsy for diagnosis and monitoring end points of the disease like fibrosis and carcinogenesis (40)

Laboratory testing during the acute phase reveals elevation in serum aminotransferases (ALT and AST) with values up to 1000-2000IU/L.The serum bilurubin concentration may be normal in patients with anicteric hepatitis.In patients who recover,normalization of serum aminotransferases usevally occurs with in one to four months.A persistant elevation of serum ALT for longer than 6 months indicates a progression to hepatitis.(41)

DNA polymerase activity,HBV DNAand HBeAg which are representative of viraemic stages of Hepatitis B,occur early in the incubation period,shortly after the appearance of HBeAg.PCR like HBeAg,HBV DNA also an indicator of viral replication and infectivity.Molecdular methods such as DNA hybridization and PCR at present used forHBV DNA testing are highly sensitive and quantitative HBV DNA level in serum reflects the degree of viral,replication in the liver and so helps to assess the progress of patients with chronic hepatitis unsder antiviral chemotherapy.

CURRENT DEBATE:
The main antigens HBsAg,HBeAg,andHBeAg each induce corresponding antibodies with exception of HBcAg.All these antigens and antibodies,together with viral DNA polymerase,can be detected in blood at various times after infection and are referred as biomarkers.HBsAg,is the first marker to appear in blood after infection.

HBsAg is usually detectable 2-6 weeks in clinical and biochemical advance of hepatitis and persists throughout the clinlcal course of the disease, HBcAg., highlevels of IgM specific anti HBc are frequently detected at the onset of clinical illness. HBeAg presence denotes high infectivity and its absence along with the presence of anti HBe, individuals low activity. HBeAg appears in blood concurrently with HBsAg,or serum afterwards. CirculatingHBeAg is an indicator of active intra hepatic viral replication and the presence in blood of DNA polymerase,HBV DNA and various reflecting high infectivity (42)

HBsAg levels are most useful in differentiating whether a patient who is HBeAg negative with low HBV DNA is truly in the inactive carrier phase.(43)

Studies have also shown that continued NA treatment is associated with increasing rates of HBsAg seroconversion to 40%. (44)

To obtain the latest national data on hepatitis B in the general population for the assessment of hepatitis B prevalence in China, and to promote effective policymaking, a systematic review and meta-analysis was performed covering the years 2013–2017.(45)

VACCINES:

The first vaccine for active immunization, introduced in 1982, was prepared from purified non-infectious 22nm spherical HBsAg particles derived from plasma of healthy carriers. In 1987, the plasma derived vaccine was a genetically engineered vaccine derived from recombinant yeast.

Current recommendations can be divided into those for pre exposure and post-exposure prophylaxis. For pre exposure prophylaxis against Hepatitis B in the setting of frequent exposure (Health workers exposed to blood, first responder public safety workers, hemodialysis patients, and staff, residents, and staff of custodial institutions for the developmentally handicapped, injection drug users, inmates of long term felicities, persons with multiple sexes partners or who have had a sexually transmitted disease, men who have sex with men, persons such as hemophiliacs who require long term, high-volume therapy with blood derivatives, households and sexual contacts of persons with chronic HBV infection, persons living in or traveling extensively in endemic areas, unvaccinated children aged less than 18, etc. The plasma-derived vaccine consists of purified inactivated HBsAg particles obtained from the plasma of chronic carriers. Now only the DNA recombinant vaccine is available. In this, the antigen particles are obtained from the yeast Saccharomyces cerevisiae through recombinant DNA technology.

MANY FACES OF HEPATITIS B:

First 90% of those infected in infancy become carriers,23% infected at 1-3 years but only 3% of those infected as University students. Worldwide there about 350 million carriers of this virus, therefore, with liver cancer causing up to 2 million deaths each year, hepatic B virus is second only to tobacco as human carcinogen. The mechanism of of carcinogenesis is not clear. Nearly all human cancers show show chromosomal integration of the virus but there is a great variation in integration site and in the number of copies of the viral genome.Very similar viruses infect woodchucks, ground squirrels and pekin ducks. In north west USA 30% of woodchucks are carriers and most develop liver cancer in later life. In this host, virus infects not only in liver cells but also lymphoid cells in the spleen, peripheral blood and thymus and pancreatic acinar cells and bileduct epithelium.(46)

MANAGEMENT:

There is no specific treatment recommended for acute hepatitis B.A high calorie diet is desirable.Treatment should be considered for patients with rapid deterioration of liver function, cirrhosis or complications such as acites,hepatoencephalopathy or hemorrhage as well as those who are immunosuppressed.For chronic hepatitis B deseases,pegelated or regular interferon alpha provides benefit in some patients.Lamivudine (3TC),a potent inhibitor of HIV and other nucleoside analogs as well as certain nucleoside analogs are active against hepatitis B.

Sceening of blood and plasma product donars for HBsAg and anti HBcAg has greatly reduced the incidence of HB in recipients.Similarly screening pregnant women and treatment of exposed newborns with hepatitis B immunoglobulin(HBIG),and vaccine have reduced vertical transmission.Safe sexual practices and avoidance of needle stick injuries or injection drug use approaches to diminishing the risk of hepatitis B infection.Both active prophylaxes and passive prophylaxis against hepatitis B infection can be accomplished Most preparations of ISG contain only moderate levels of anti-HBs;however,specific HBIG with titers of hepatitis B antibody is now available.HBIG is prepared from sera of subjects who have high titers of antibody toHBsAg but are free of the antigen itself.

CONCLUSION:

It has taken several centuries to identify the causes of the epidemic jaundice that increased after early attempts to initiate public vaccination programs and with the widespread application of blood transfusions from unrelated donors. (47)

Reactivation of HBV replication has a negative impact on the clinical course of patients with hemo-lymphoproliferative malignancies, because of its significant morbidity and its potential to induce a worse prognosis or even a fatality. However, no shared effective solution has been decided worldwide to date, nor has a uniform standard of screening, treatment or prevention been established. Given the efficacy of nuclei side analogs against HBV, administered as treatment or prophylaxis is reported for the patients at risk. All patients should be evaluated for serum HBsAg, anti-HBc antibody, HBV DNA and liver enzymes before any immunosuppressive therapy are initiated. In recent years, national and international guidelines have recommended HBV screening before starting chemotherapy.

The risk posed by individual treatment regimens should be carefully assessed to establish the need for antiviral prophylaxis or treatment and the duration of antiviral drug administration. For the patients identified as requiring antiviral treatment or prophylaxis, anti-HBV nucleoside/nucleotide analogs with a high genetic barrier to viral resistance is recommended, especially for those at a high risk of HBV reactivation and when longterm immunosuppressive treatment is planned.(48)

The outcome of HBV infection is heavily dependent on age. In adults,nearly 2/3 of new infections are subclinical and about 1/3 lead to icteric hepatitis.At younger age the frequency of the disease is lower. Thus,most infections in infants are asymptomatic. About 1% of patients with acute hepatitis B develop fulminate hepatic failure.(49)

REFERENCES:

1. Leu, Korea Centers for Disease Control & Prevention. Korea National Health and Nutrition Examination Survey (KNHANES) 2016 [Internet]. Cheongju (KR): KCDC, 2016
2. Cho EJ, Kim SE, Suk KT, et al. Current status and strategies for hepatitis B control in Korea. Clin Mol Hepatol 2017;23:205-211.
3. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of the worldwide prevalence of chronic hepatitis B virus infection: A systematic review of data published between 1965 and 2013. Lancet 2015; 386: 1546-1555
4. Sagnelli C, Macera M, Pisaturo M, Zampino R, Coppola M, Sagnelli E. Occult HBV infection in the oncohematological setting. Infection 2016; 44: 575-582
5. Hoofnagle JH. Reactivation of hepatitis B. Hepatology 2009; 49: S156-S165
6. Meireles C, Marinho RT, VanDamme P, Three decades of hepatitis B control with vaccination.World.Heptol 2015;7:2127-32
7. WHO,Immunization coverage.2016.Available at htpp//www whoint/immunization/monitoring.Surveilance/routine/coverage.Index 4 html accessed April 2017.
8. Glynn SA, Kleiman SH, Wright DJ, Busch MP,2002.International application of the incidence rate/window period model transfusion 42(8):966-972
9. Liu GC,Liu GY et al.Bayesian analysis on the prevalence of HBV infection among Chinese volunteers blood donor PLoS one 2013 8e/79203
10. Qian HG,Zhang J,LengJIT,et al.Association of hepatitis B virus infection and cirrhosis with liver metastasis in colorectal cancer.Zhonghua Wei Chang Wai Ke Za Zhi 2010; 13:202-4
11. Poh Z, Goh BB, Chang PE, Rates of cirrhosis and hepatocellular carcinoma in chronic hepatitis B and the role of surveillance a 10-year follow up of 673 patients.Eur.J.Gastroenterol Hepatol 2015,27:638-43
12. Wiktor SZ, Hutin YJ , The global burden of viral hepatitis; better estimates to guide hepatitis elimination efforts.Lancet,2016 :388-:1030
13. VijayadevaV,spreading,Moorman AC,et al.Hepatitis B Virus infection testing and prevalence among Asian and Pacific islanders. Am.J.Manag.care 2014,20e:98e104
14. Yue X, Black CL, O'Halloran A, Lu PJ, Willium WW, Nelson NP.Hepatitis A and Hepatitis B vaccination coverage among adults with chronic liver disease.Vaccine,2018;36:1183-9.
15. W. Demsiss, A. Seid, T. Fiseha, and I. Chemin, "Hepatitis B and C: Seroprevalence, knowledge, practice and associated factors among medicine and health science students in Northeast Ethiopia," PLoS ONE, vol. 13, no. 5, p. e0196539, 2018.
16. Gill US, Peppa D, Micco L, et al. Interferon-alpha induces sustained changes in NK cell responsiveness to hepatitis B viral load suppression in vivo. PLoS Pathog 2016; 12: e1005788.
17. CDC. Hepatitis B. Available online: https://www.cdc.gov/hepatitis/hbv/bfaq.htm#overview (accessed on 1 January 2019.
18. World Health Organization. Hepatitis B. Available online: www.who.int/news-room/fact-sheets/detail/hepatitis-b (accessed on 1 January 2019
19. Frodsham, A. J. Host genetics and the outcome of hepatitis B viral infection. Transplant immunology 14, 183–186,. 2005
20. Manolio, T. A. et al. Finding the missing heritability of complex diseases. Nature 461, 747–753,
21. Barbara Mühlemann; et al. 2018. "Ancient hepatitis B viruses from the Bronze Age to the Medieval period". Nature. 557(7705): 418-423
22. Ben Guarino (9 May 2018). "New strains of hepatitis B virus discovered in ancient human remains". The Washington Post. 2018.
23. Ross, Zoe Patterson; Klunk, Jennifer; Fornaciari, Gino; Giuffra, Valentina; Duchêne, Sebastian; Duggan, Ana T.; Poinar, Debi; Douglas, Mark W.; Eden, John-Sebastian 2018. "The paradox of HBV evolution as revealed from a 16th-century mummy". PLOS Pathogens. 14 (1): e1006750.
24. Paraskevis D, Magiorkinis G, Magiorkinis E, Ho SY, Belshaw R, Allain JP, Hatzakis A 2013. "Dating the origin and dispersal of hepatitis B virus infection in humans and primates". Hepatology. 57 (3)
25. Rasche A, Souza BF, Drexler JF.2016. "Bat hepadnaviruses and the origins of primate hepatitis B viruses". Current Opinion in Virology. 16: 86–94.
26. Bouckaert R, Simons BC, Krarup H, Friesen TM, Osiowy C 2017. "Tracing hepatitis B virus (HBV) genotype B5 (formerly B6) evolutionary history in the circumpolar Arctic through phylogeographic modeling". PeerJ. 5: e3757.
27. Ben Guarino 2018. "New strains of hepatitis B virus discovered in ancient human remains". The Washington Post. Retrieved 9 January 2018.

28. John B Carter and vnetia A Saunders,Virology principles and applications,2014,pp224.
29. Richard V.Goering,Haxel M,Dockrell et al.MimsMedical microbiology 5 th Ed,Elsavier,2013
30. KennethJ.Ryan,C.George Ray,NafeesAhmed,W.Lawrence Drew,James,Sherris Medical microbiology 5th Ed,.Plorde.Mc Graw hill Medical,2010.
31. Centers for disease control and prevention (CDC) updated CDC recommendations for the management of hepatitis B virus infected health-care providers and students.MMWR.Recommn.Rep.2012;61:1-12
32. Timothy M,Block,Stephen locarnini et al.Use of current and new end points in the evaluation of experimental Hepatitis B therap[eutics.2017,Clinical infectious disease.
33. Lok AS, McMahon BJ; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Chronic hepatitis B. Hepatol 2001;34:1225-41.
34. Boyd A, Duchesne L, Lacombe K, Research gaps in viral hepatitis.J Int AIDS Soc. 2018 Apr;21 Suppl 2:e25054.
35. FattovichG,Bortolotti F,Donato F, Natural history chronic hepatitis B,Special emphesis on disease progression and prognostic factors.J.Hepatol 2008;48:335-352
36. Sartorius K, Sartorius B, Aldous C, Govender PS, Madiba TE. Global and country underestimation of hepatocellular carcinoma (HCC) in 2012 and its implications. Cancer Epidemiol. 2015;39 (3):284–290.
37. Spradling PR,Rupp L,et al.Chronic hepatitis cohort study investigators.HBV and BCV infection among 1.2 million persons with access to care.Factors associated with testing and infection prevalence.Cli.Inf.Dis 2012;55:1047-55
38. Singal AG,Tiro J,et al.J.hepatocellular carcinoma surveillance among patients with cirrhosis in a population based integrated health care delivery system.J Clin.Gastroenterol 2017;51:650-5
39. Jonas M, M,Reddy RK,De medicine M et al. Hepatitis B in a large municipal obstetrical population.Charecterization perinatal transmission.Amm.J. Gastroenterol.85;277:280.1990
40. Mamun Al-Mahtab,SM Fazle Akbar,Salimur Rahman,Comprehensive text book of hepatitis B-Japee brothers ,Medical publishers (p) Ltd,2011.
41. Jereny Farrar,Peter J.Hotez,et al.Manson's tropical diseases 23 rd edn,Elsavier,saunders,2014,Prited in China.
42. Surindra Kumar,Essentials of Microbiology Health sciences publisher,Jaypee brothers Medical Publisher,2016,pp 470,.
43. Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: A 5-year open-label follow-up study. Lancet 2013;381:468-475
44. Buster EH, Flink HJ, Cakaloglu Y, Simon K, Trojan J, Tabak

F, et al. Sustained HBeAg and HBsAg loss after long-term fol- low-up of HBeAg-positive patients treated with peginterferon alpha-2b. Gastroenterology 2008;135:459-467.

45. Hie-Won Hann, Advances in the Management of Hepatitis B Virus Infection, Gastroenterol Hepatol (N Y). 2014 Jun; 10(6): 384–386
46. .Richard.V.Goering,Hazel M,Dockrell,Mark Zuckerman et al. Mims'Medical microbiology 5 ED,Int.ED,Elsavier,2013.
47. Caterina Sagnelli, Mariantonietta Pisaturo, Federica Calò, Salvatore Martini, Evangelista Sagnelli, Nicola Coppola, Reactivation of hepatitis B virus infection in patients with hemolymphoproliferative diseases, and its prevention World J Gastroenterol 2019 July 14; 25(26): 3299-3312
48. Y.Kim, The national academy report on the elimination of viral hepatitis,An infectious disease,Physician perspective,Clinical infectious disease (CID),2017 :65,pp 7092.
49. . Sandhya Kamath,Sidharth.N.Shah et al. API.Text book of Medicine,11 ED,Vol-2 pp1803,2019.